Ethical Concerns Related to Developing Pharmacogenomic Treatment Strategies for Addiction

Pharmacogenomics (PGx) research is poised to enable physicians to identify optimally effective treatments for individual substance abusers based on their genetic profiles. This paper addresses ethical issues related to PGx treatment strategies for addiction, focusing especially on the use of race variables in genomics research and ensuring equitable access to novel PGx treatments. Unless the field addresses the ethical challenges posed by these issues, PGx treatment innovations for addiction threaten to exacerbate already dramatic disparities in the burden of drug dependence for minority and other underserved populations.

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Expectations are high that pharmacogenomics (PGx) research will soon enable physicians to use genetic profiles to identify the safest and most effective treatments for each individual patient. Recent articles have addressed a range of important ethical considerations in translating emerging PGx research into clinical practice (Buchanan et al., 2002; Robertson et al., 2002; Clayton, 2003; van Delden et al., 2004; Corrigan, 2005; Lee, 2005; Ossorio and Duster, 2005; Roden et al., 2006; Marx-Stolting, 2007; Fitzgerald, 2008; Haga and Burke, 2008; Peterson-Iyer, 2008; Fleeman and Dickson, 2009), and a few have addressed issues related to PGx treatment strategies for addiction specifically (Shields et al., 2004; Caron et al., 2005; Munafo et al., 2005; Shields and Lerman, 2008). Largely missing from these analyses has been consideration of distributive justice and health disparities.

Although eliminating health disparities is one of two primary goals of Healthy People 2010 (U.S. Department of Health and Human Services, 2000), the substance abuse field has made far more progress in documenting disparities than in reducing them (Fiscella et al., 2000; Hargraves et al., 2001; Kressin and Petersen, 2001; Fiscella et al., 2002; Institute of Medicine, 2002a; 2002b; Schneider et al., 2002; Saha et al., 2003). Compared with whites, racial and ethnic minorities have a greater need for substance abuse treatment (National Institute on Drug Abuse, 2003) and are less likely to have access to it (Wells et al., 2001). The "treatment gap," defined as the proportion of a population who are in need of drug or alcohol treatment but have not received any in the past year, increased for all nonwhite racial/ethnic groups between 2002 and 2009, with the exception of Asian Americans (Schmidt and Mulia, 2009).

In this paper, I review major ethical issues pertinent to PGx research and its translation into practice, focusing on the context of addiction. Reflecting concerns for distributive justice, I pay particular attention to ways in which PGx research and treatment strategies may exacerbate disparities in the burden of addiction. Powers and Faden (2006) argue that individuals and groups who have been "systematically disadvantaged" by our health care system have a particular claim on public resources and investments.

Following the overview of major issues, I focus on two areas that are critical to ensure that minority and other underserved populations benefit equally from PGx advances in addiction treatment: using race variables in genomics research (Institute of Medicine, 2002a; 2002b) and ensuring equitable access to novel PGx treatments once they become widely available. These two issues have the greatest potential implications for just distribution of the benefits of PGx research on addiction and might be considered essential bookends in the examination of ethical issues related to the long trajectory from PGx research to improved health outcomes. Unless the field proactively addresses the ethical challenges they pose, innovations in addiction treatment will likely widen the existing disparities in treatment outcomes and the burden of drug dependence.

ETHICAL ISSUES IN PHARMACOGENOMICS RESEARCH

Privacy and the Potential for Discrimination

The advent of genomic medicine has raised unprecedented concerns about privacy and confidentiality, two key standards in medical research and practice that reflect the fundamental values of beneficence and the responsibility to do no harm (Beauchamp and Childress, 2001). Genetic information is unique relative to other medical information in at least two respects that increase its sensitivity. First, information about an individual's genome simultaneously provides information about his or her relatives (Buchanan et al., 2002; Robertson et al., 2002; Nuffield Council of Bioethics, 2003). Second, many genetic variants are pleiotropic—that is, they have clinical relevance for more than one condition. A classic example of pleiotropy is a variant of the apolipoprotein (APOE) gene that influences both cardiac care and the risk of late onset Alzheimer's disease (Hayden, 2008). Accordingly, some medical professionals and ethicists have worried that genetic research could usher in new forms of stigmatization and discrimination by health insurers or employers against individuals who are identified as having increased risk of specific conditions or being nonresponders to medication.

These concerns may be amplified in the context of addiction. Substance abusers, especially those who are poor, are among the most stigmatized individuals in society (Room, 2005). The process of matching substance abusers to optimal PGx treatments could potentially expose them to still further devaluation, depending on the genetic variants used to match them to the optimal choice of medication. Gene variants implicated in nicotine dependence, for example, have been associated with increased risk of becoming addicted to cocaine and alcohol, and with psychiatric conditions, including Tourette's syndrome, post-traumatic stress disorder, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, anxiety, paranoia, depression, and suicide (Shields et al., 2005).

The advent of genomic medicine has raised unprecedented concerns about patient privacy and confidentiality.

Although some concerns have been allayed by the passage of the Genetic Information Nondiscrimination Act (H.R. 493, 110th Cong., 2nd Sess., 2008) and the Patient Protection and Affordable Care Act (H.R. 3590, 111th Cong., 2nd Sess., 2010), many analysts still consider privacy and genetic discrimination protections to be inadequate (Hudson et al., 2008; Slaughter, 2008; McGuire and Majumder, 2009). Health care reform may soon address concerns that individuals will be denied insurance coverage or charged higher premiums based on genetic status, but more diffuse manifestations of social stigma or discrimination may be harder to curtail.

Data Storage and Use

The sensitive nature of genetic information highlights the need for responsible storage in biobanks and medical records and poses challenges for informed consent procedures (Nuffield Council of Bioethics, 2003; Corrigan, 2005; Peterson-Iyer, 2008). Large banks of genetic data are indispensable for PGx studies that explore how genes interact with each other and the environment to produce health effects, but the storage and use of such data raise concerns (Clayton, 2005; Corrigan, 2005; Haga and Burke, 2008). One challenge has been clarifying whether the scope and intent of participants' informed consent for participation in a past study permits the use of their genetic data in new studies that may not have been envisioned at the time the consent was provided. The U.S. Department of Health and Human Services has advanced policy recommendations intended to minimize harm to and

respect the informed wishes of study participants while facilitating the aggregation of diverse data sets needed to advance science (U.S. Department of Health and Human Services, 2008). Consumers have expressed a preference for tiered consent schemas that allow individuals to specify the level of data sharing permitted with respect to their genomes (McGuire et al., 2008; Peterson-Iyer, 2008).

Beyond research, as more patients undergo genetic testing in clinical settings, there is growing concern about the storage and use of genetic test results (Buchanan et al., 2002; Robertson et al., 2002; Nuffield Council of Bioethics, 2003; Schubert, 2004; Corrigan, 2005; Munafo et al., 2005; Marx-Stolting, 2007; Haga and Burke, 2008; Henrikson et al., 2008; Peterson-Iyer, 2008). Who should have access to individuals' genetic information, and how can it be protected against unauthorized access, particularly as electronic health records (EHRs) become more widespread? The EHR concept aims to make relevant patient information readily available to all treating clinicians to increase the coordination of health care, reduce harm and waste, and increase quality and efficiency.

However, the question of how much of patients' genetic status data should be included in EHRs, and under what restrictions, has not yet been systematically addressed. I have argued elsewhere (Shields et al., 2005) that the sensitive nature of addiction-related phenotypes warrants increased scrutiny regarding processes for storing and communicating information about patients' genetic status and that prudent policies should be based on the most potentially stigmatizing information generated by a given genetic test.

Merely describing a new test as "genetic" reduced physicians' willingness to offer it to patients.

Answers to these questions will become increasingly urgent and financial incentives aimed at increasing EHR use within the U.S. health care system promise to accelerate widespread adoption of EHR systems nationally. (Currently only 13 percent of physicians [DesRoches et al., 2008] and 8 percent of hospitals (Jha et al., 2007; 2008) have EHR systems in place.)

Beyond the clinic, the proliferation of "home-brew" genetic tests (manufactured with noncommercial reagents and not approved by the U.S. Food and Drug Administration) (Buchanan et al., 2002) and the accumulation of genetic information by private companies that market genetic tests directly to consumers (Wolfberg, 2006; Hudson et al., 2007; Hogarth et al., 2008) pose further challenges to ensuring against irresponsible use of genetic test results.

Provider Readiness to Use PGx Treatments

Although genetically guided treatment has been incorporated into routine practice in some specialties for many years (e.g., oncology), the fact that addiction is most often first treated in primary care settings will pose substantial challenges for clinical integration, with practices serving poor and minority patients likely to face greater challenges than others (Bach, 2004). Few primary care physicians (PCPs) have formal training in genetics, which constitutes a barrier to clinical integration of novel PGx treatment strategies. Nationally, only 4 percent of PCPs report feeling very prepared to counsel patients considering genetic testing, and 5 percent feel very confident in interpreting genetic test results (Shields et al., 2005). In studies addressing challenges to incorporating genetically tailored smoking-cessation treatment, merely describing a new test to tailor smoking-cessation treatment as "genetic" (vs. "nongenetic") reduced physicians' willingness to offer it to their patients (Shields et al., 2005). Informing physicians that the same genotypes that likely would be used to match patients to optimal treatment were also associated with increased risk of becoming addicted to substances besides tobacco markedly dampened their enthusiasm for testing (Levy et al., 2007).

Understanding the genetics of complex behaviors such as addiction will place particular demands on physicians. Future PGx approaches to identify treatment responders and nonresponders will likely involve assessing multiple genes in multiple interacting neurobiological pathways that mediate a medication's pharmacodynamic effects, as well as genetic variants in drug metabolizing enzymes (Munafo et al., 2005; Rutter, 2006). PGx practitioners will need to evaluate not only the relative importance of multiple gene variants, but also potential interactions of these polymorphisms with other drugs and environmental exposures. Clear and accessible guidelines will be essential to assist PCPs and allied health professionals with addiction treatment decisions (Freedman et al., 2003), as will decision support available through EHR systems.

Minorities with substance dependence are more likely than whites to be treated in primary care settings rather than specialty alcohol or drug treatment programs (Schmidt et al., 2007). Therefore, preparing PCPs to implement new PGx treatments for addiction will have a direct bearing on disparities. To achieve this preparation, infrastructure and capacity will need strengthening. Small primary care practices, which currently make up 50 percent of all practices nationally (Burt et al., 2005), are

especially in need of infrastructure development. They consistently lag behind in adoption of new technologies, such as health information technology (DesRoches et al., 2008). Ensuring that PCPs have access to EHR systems that have the decision support platforms they need will be essential to guarantee that future PGx treatment strategies for addiction reach underserved patients in need of substance abuse treatment.

Patients' Willingness to Undergo Genetic Testing

Ultimately, patients will benefit from PGx treatment strategies only if they are willing to undergo genetic testing. Therefore, it is critical to understand how patients' knowledge, attitudes, and experiences may affect their willingness to participate in PGx-based medicine. Several studies have documented a general lack of awareness, knowledge, and understanding of genetic testing (Bluman et al., 1999; Donovan and Tucker, 2000; Kinney et al., 2000; Singer et al., 2004), especially among low-socioeconomic status (SES) and minority communities (Hughes et al., 1997; Mogilner et al., 1998; Lipkus et al., 1999; Kinney et al., 2001; Armstrong et al., 2002; Peters et al., 2004; Singer et al., 2004; Bates et al., 2005; Murphy et al., 2009; Suther and Kiros, 2009). Individuals' interest in genetic testing rises with educational level (Andrykowski et al., 1996; Mogilner et al., 1998; Lerman et al., 1999; Peters et al., 2004), and those with higher levels of education express fewer concerns about possible misuse of genetic information (Suther and Kiros, 2009).

Mistrust is a major factor affecting patients' willingness to undergo genetic testing, especially within minority communities that have historically experienced discrimination. Although some studies have found no racial differences in willingness to undergo genetic testing (Lacour et al., 2008), several have shown that African Americans are more likely than other groups to believe that genetic test results will be misused (Singer et al., 2004; Suther and Kiros, 2009), be used to label their racial/ethnic group as inferior (Thompson et al., 2003; Peters et al., 2004), or lead to racial discrimination (Zimmerman et al., 2006). African Americans are far more likely than other groups to see racism as a significant problem in health care (Lillie-Blanton et al., 2000) and consistently report racial discrimination in obtaining medical care (Henry J. Kaiser Family Foundation, 1999; Klassen et al., 2002; Smedley et al., 2003). The legacy of the Tuskegee syphilis study (Gamble, 1997) and of insurance and employment discrimination based on the results of sickle cell screening (Bowman and Murray, 1990; King, 1992a; 1992b) remain salient within the African American community. African Americans tend to have negative views about participation in medical research and to be skeptical that their community will share in any positive benefits of genetic research (Corbie-Smith et al., 1999). Latinos also have expressed mistrust about genetic testing. In a national survey of 1,724 individuals, African Americans were 66 percent and Latinos were 58 percent more likely than whites to have concerns about potential misuse of genetic information (Suther and Kiros, 2009).

Religious orientation also shapes attitudes toward genetic testing. Regular church attendance and reliance on God in health care decisionmaking correlate negatively with perceived benefits and acceptance of genetic testing, and are traits more common among African Americans than whites (Singer et al., 2004). Catholics are less likely to endorse positive views of genetic testing, and Latinos are more likely to be Catholic (Singer et al., 2004). In summary, outreach and communication strategies tailored to the needs, preferences, and cultures of minority and low-SES communities will be necessary to ensure that new PGx treatment strategies for addiction are translated into practice in ways that improve treatment outcomes for all patients and do not exacerbate existing racial and SES disparities.

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THE USE OF RACE VARIABLES IN PGx RESEARCH

While the majority of ethical analyses of PGx have focused on the ethical imperative to do no harm at the level of the individual patient, two key issues have particular salience for the notion of distributive justice and the potential of PGx research to translate into harm or benefit for minority communities. The first relates to how race variables are used, interpreted, and communicated in PGx research. Numerous articles and editorials have debated the implications of using race variables in the design of genetic research studies, data interpretation, results communication, and impact on broader societal concerns (Osborne and Feit, 1992; Bhopal, 1997; Kaufman and Cooper, 2001; Lee et al., 2001; Schwartz, 2001; Wood, 2001; Burchard et al., 2003; Cooper et al., 2003; Haga and Venter, 2003; Kaplan and Bennett, 2003; Stevens, 2003; Cooper, 2004; Shields et al., 2005). There are three major drawbacks to using self-identified racial variables in PGx research on addiction:

- self-identified race is an inadequate proxy for human genetic heterogeneity;

- focus on race obscures understanding the role of environmental influences; and
- the use of race variables increases the potential for discrimination.

PGx research on addiction can help to disentangle the genetic, social, and environmental influences underlying "racial" differences in drug dependence and treatment response.

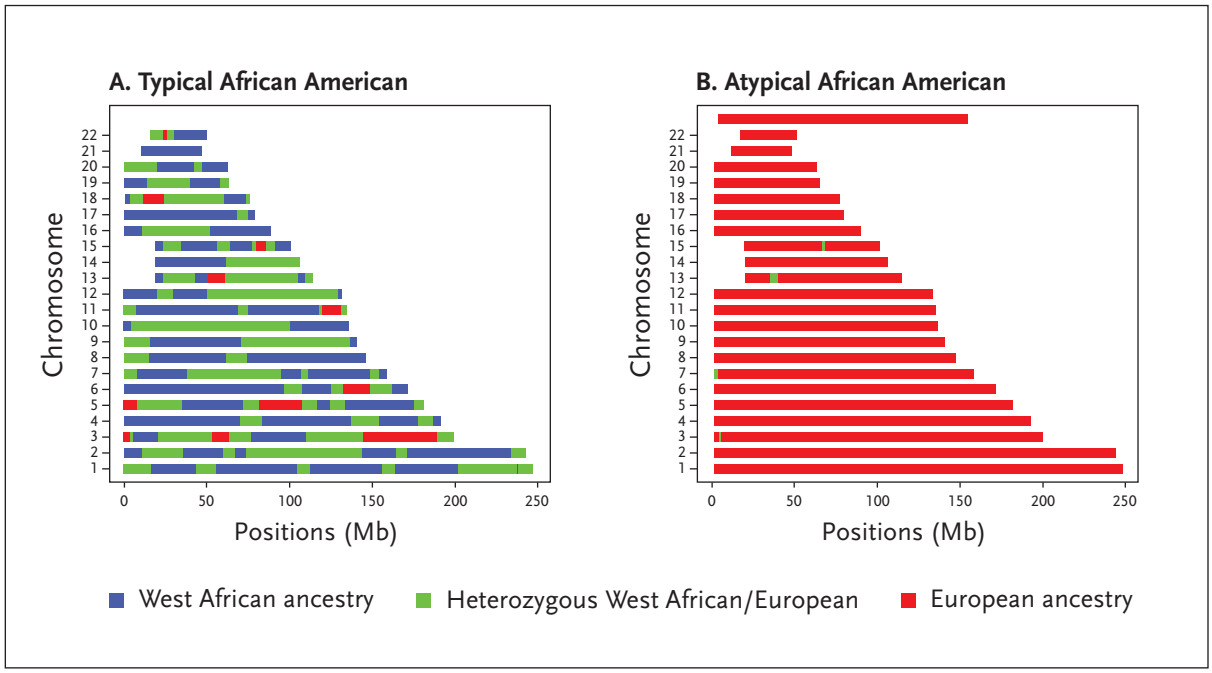
Race Versus Genetic Heterogeneity

Racial categories mask genetic diversity, so that PGx treatments based on research using racial categories could be ineffective or even harmful for many individuals. Self-identified racial categories such as those set forth by the Office of Management and Budget (OMB Directive 15, National Institutes of Health, 2001) and used in the federal census are a rough and poorly characterized proxy for defining an amalgam of influences related to social identity, geographical ancestry, and social status (Shields et al., 2005). More scientifically precise methods are available for measuring population structure (Novembre et al., 2008; Bryc et al., 2010) and should be used.

The limited usefulness of self-identified racial categories is perhaps most clearly illustrated by the term "African American," since genetic heterogeneity is greater among self-identified African Americans than among most other self-identified groups. For example, Bryc and colleagues (2010) analyzed fine-scale population structure among 146 individuals representing 11 different populations in West and South Africa; 57 Yorubas genotyped as part of the International HapMap project; 365 self-identified African Americans from throughout the U.S.; and 400 individuals in Europe. The researchers used fine-scale genetic mapping to infer the mix of African ancestries in the African Americans and to identify West African populations closest to the ancestral populations of African Americans. Although the African Americans as a group averaged 77 percent West African ancestry, individual African Americans ranged from less than 1 percent to more than 99 percent West African ancestry (Figure 1; Bryc et al., 2010). Such diversity compels extreme caution in prescribing clinical guidelines or developing warnings for adverse drug responses for "African Americans."

Fine-scale mapping of European cohorts has identified genetically distinct subpopulations (Lao et al., 2008; Novembre et al., 2008; McEvoy et al., 2009) that would be missed if the general terms "European" or "white" were used in analyses. For example, using genotype data from 197,146 loci from 1,387 individuals of European ancestry from the Population Reference Sample, Novembre and colleagues (2008) were able to identify genetically

FIGURE 1. African and European Ancestry in African Americans



A representative individual among 365 self-identified African Americans had 73.5 percent West African ancestry, as revealed by genomic analysis (A). West African ancestry ranged from less than 1 percent in one individual (B) to over 99 percent. Blue bands = West African ancestry in both maternal and paternal chromosomes; green = West African ancestry in one chromosome and European ancestry in the other; red = European ancestry in both maternal and paternal chromosomes.

distinct subpopulations among French-, German-, and Italian-speaking groups in Switzerland.

With new technologies (e.g., the Affymetrix 500k SNP chip) now widely available to identify nuanced differences in population structure, the use of gross racial/ethnic categories in PGx studies or treatment guidelines becomes ethically problematic. Although technical limitations or resource constraints sometimes will limit a research team's ability to do such fine-scale mapping, its availability raises the bar for all genomics researchers.

Race, Genes, and Environmental Exposures

The use of self-identified race as a proxy for human genetic heterogeneity in PGx studies of addiction is especially problematic when studies do not measure other social and physical environmental exposures that track with race in America. First, such analyses increase the likelihood that the self-identified race variable will be statistically significant and thus reify self-identified race as the most relevant frame for understanding differences in response to addiction treatment. Second, such research designs miss the opportunity to disentangle complex genetic, social, and environmental interactions (Hernandez and Blazer, 2006) or epigenetic effects (Olden et al., 2011) that affect the progression to addiction, response to treatment, or a drug's kinetic effects.

Potential for Worsening Discrimination

The poor specificity of racial/ethnic variables in PGx research is often compounded by failure to measure social and environmental exposures that track with self-identified race in America, thereby masking important gene-environment effects. Missing these effects means missing an opportunity to disentangle the complex social, environmental, behavioral, and genetic factors that interact to create disease and determine treatment outcomes. PGx studies of addiction would likely be far more informative if population structures were finely mapped and if other social and environmental exposures that often track with "race" were measured independently. Such research would also be more likely to yield insights useful for addressing disparities. Low-SES and minority patients' experiences subject them to a distinct confluence of social and environmental exposures that likely interact with clinically relevant genotypes.

PGx analyses that frame new knowledge in terms of "racial differences" in allele frequencies relevant to disease risk or drug response continue a long and painful history of comparative racial science in the U.S. Such science leads to headlines such as "Blacks more likely to have gene X associated with addiction," and has almost always been used to allege that African Americans are inferior (King, 1992a; 1992b). When "racial" differences intersect with socially charged phenotypes, such as those related to addiction or mental illness, physicians shy away from genetic testing for fear that results may lead to discrimination against their patients (Levy et al., 2007).

The reporting of higher frequencies of genotypes associated with addiction to nicotine, cocaine, and other substances among African Americans relative to whites has a particularly problematic intersection with existing racial stereotypes. For example, several studies have documented physicians' inadequate prescribing of pain medications for African American patients relative to white patients with similar conditions and illness severity, noting physician concerns about potential drug abuse by minority patients (Cleeland et al., 1997; Todd et al., 2000). It is not surprising, therefore, that African Americans tend to be more concerned than other groups that genetic test results will be used to discriminate against them or their community.

ACCESS TO NOVEL PGx ADDICTION TREATMENTS

The second "bookend" of the PGx research trajectory that has important implications for distributive justice is ensuring equal access to new PGx applications once they are validated and available to be used in clinical settings. To the extent that novel PGx treatments for addiction improve outcomes by an order of magnitude over previous regimens, it will be especially important to ensure equal access to these markedly improved treatments; otherwise, these advances will merely widen the existing disparities gap in substance abuse treatment.

A successful strategy for ensuring equal access to PGx information and treatments must engage patients, providers, and policymakers.

Disparate access to new technologies and treatments is certainly not a new issue; widespread and persistent gaps have been documented (Smedley et al., 2003). A successful strategy for ensuring equal access to PGx information and treatments must engage patients, providers, and policymakers. The benefits of individualized treatment must be communicated to minority and low- SES patients in ways that are culturally competent, accessible, and appropriate, and that mitigate concerns about genetic testing (Betancourt, 2004). Modes of dissemination must be carefully considered. The recent Health Information National Trends Survey indicated that media saturation on a given topic reaches similar percentages of people in all socioeconomic position

(SEP) classifications; in the absence of media saturation, however, people in higher SEP groups have better access to other sources of information, such as physicians or informed friends (Viswanath et al., 2006). Diffusing information about genomic medicine is challenging in any context. Even with the establishment of high-risk guidelines for hereditary breast and ovarian cancer in the 1990s (American Society of Clinical Oncology, 1996; Daly, 1999) and the development of *BRCA1/2* testing to assess hereditary breast cancer risk, only 10.7 percent of women who were appropriate candidates for genetic testing according to national guidelines had ever even discussed the possibility of genetic testing with their doctor or another health professional (Levy et al., 2009).

Ensuring that new PGx treatments reach minority and low-SES patients will require investment in the infrastructure and clinical capacity of the providers who serve them. One potential strategy for reaching minority patients is to concentrate on minority-serving providers. Approximately 22 percent of physicians, for instance, care for 80 percent of all black Medicare beneficiaries in the U.S. (Bach et al., 2004). Focusing on minority-serving providers may be an especially effective strategy in the context of substance abuse treatment, given that minorities with substance dependence are more likely than whites to be treated in primary care settings rather than specialty alcohol or drug treatment programs (Schmidt et al., 2007).

The more effective PGx treatments for addiction are, the more important it will be to ensure that minority and underserved populations share in their benefits.

The challenges related to physicians' preparedness to incorporate PGx treatments into practice will be especially keen in these settings that disproportionately serve poor and minority patients. In a national survey of PCPs, those who served the highest proportions of minority patients (i.e., ranking in the top 20 percent of the national distribution) were significantly less likely to have ever ordered a genetic test to assess risk for breast cancer (18 percent vs. 29 percent; $P = 0.01$), colon cancer (11 percent vs. 18 percent, $P = 0.05$), or Huntington disease (6 percent vs. 18 percent; $P < 0.001$) compared with those serving fewer minority patients (Shields et al., 2008). Among community health centers (CHCs), which serve 1 in 4 poor, 1 in 7 uninsured, and 1 in 10 minority patients (National Association of Community Health Centers, 2005), only 4.3 percent have the capacity to deliver genomics services (Shields et al., unpublished data). These findings are consistent with several studies documenting safety net providers' difficulty accessing specialty care for their patients (Felt-Lisk et al., 2002; Felland et al., 2003).

Targeted financial support is also likely to be needed. The current average CHC operating margin is less than 1 percent (McAlearney, 2002; National Association of Community Health Centers, 2005), leaving scarce resources to expand genetics services. Safety net hospitals and clinics that disproportionately serve minority patients are similarly strapped (Lewin and Altman, 2000; Varkey et al., 2009). Increased fiscal pressures have decimated many state Medicaid programs, the primary source of health insurance for low-income families, and many of these programs have restricted prescription drug benefits (Crowley et al., 2005; Kaiser Commission on Medicaid and the Uninsured, 2010). Low-income Americans will not have equal access to PGx treatments if Medicaid does not provide the same coverage for these services as private insurers.

The over-representation of minorities dependent on substances among the uninsured also threatens to exacerbate disparities. According to data from the National Alcohol Survey, for example, 28 percent of African Americans and 41 percent of Hispanics with a current substance dependence diagnosis are uninsured, compared with only 19 percent of whites with such a diagnosis (Schmidt and Mulia, 2009). Uninsured adults have tremendous difficulty accessing care for alcohol, drug abuse, and mental health problems (Wells et al., 2002). Uninsured adults and those on Medicaid have the greatest unmet need and delays in care (Wells et al., 2002). While health care reform may reduce some of these barriers, many will surely remain. Targeted supplemental reimbursement will most likely be needed to enable safety net providers to ensure access to new PGx treatments for addiction.

CONCLUSION

PGx research is making remarkable progress in identifying genetic variants associated with increased vulnerability to drug dependence and variable response to substance abuse treatment. The next generation of studies, now just beginning, will tackle measurement of gene-gene and gene-environment interactions that affect susceptibility and treatment responses. The sensitive and stigmatized nature of addiction phenotypes, in concert with pleiotropic associations of key genotypes with other socially stigmatized conditions, warrants great care in the handling of reporting and use of PGx test results. It is hard to overstate the importance of finding ways to communicate the complex and continuous nature of human genetic variation to the general public and

USE OF RACE VARIABLES IN PGx RESEARCH ON ADDICTION

Traditional racial categories are ill-suited to pharmacogenomics (PGx) research, especially in studies that examine sensitive phenotypes such as drug abuse and addiction. From this viewpoint, I assessed the use of race variables in all 2007–2010 PGx addiction publications included in a recent comprehensive review conducted by Mroziewicz and Tyndale (2010).

All 32 human studies used self-reported race/ethnicity variables for participant recruitment. Two required a more stringent self-reported definition: Berrettini and colleagues (2008) enrolled only participants "for whom the four grandparents were of European origin," and Le Marchand and colleagues (2008) enrolled only those "having both parents of Japanese or European ethnicity, or of any amount of Native Hawaiian ancestry."

The thorny issues related to successfully recruiting a diverse study population and resolving the tensions between self-identified race and population structure have led many researchers to sidestep the issue completely by studying only "European" or other samples assumed to be genetically homogeneous. Eighteen of the 32 studies took this route by recruiting all participants from "single" populations. Ten studies included only "European" or "Caucasian" subjects, with no further information given (Audrain-McGovern et al., 2007; Bierut et al., 2007; Lee, et al., 2007; Vanyukovet al., 2007; Amoset al., 2008; Berrettini et al., 2008; Conti et al., 2008; Uhl et al., 2008; Oroszi et al., 2009; Pillai et al., 2009). Six other studies were conducted with "Europeans" or "Caucasians" from specified locations (e.g., Northern Poland [Sieminska,et al., 2008]; Croatia [Mokrovic et al., 2008]; and Finland [Arias et al., 2008]); and persons of "European descent" from St. Louis, Detroit, Minneapolis, and Australia (Saccone et al., 2007). Other "single" population studies included Koreans (Kim et al., 2009) and Han Chinese from Taiwan (Huang et al., 2007). The most common rationale provided for limiting analyses to a "single" population was to "minimize the potential bias resulting from ethnic admixture" (Audrain-McGovern et al., 2007; Huang et al., 2007; Lee et al., 2007; Amos et al., 2008; Berrettini et al., 2008; Conti et al., 2008; Hung et al., 2008; Lerman et al., 2010).

Of the 32 studies in our sample, only seven (one multiethnic and six "single" population) conducted additional analyses to assess population structure and admixture using ancestry-informative markers (AIMs). For example, a multi-ethnic study used 207 AIMs to "verify self-reported ancestry and assess admixture within racial groups," using an inclusion threshold of at least 80 percent ethnic identity (Sherva et al., 2008). Saccone and colleagues (2007) similarly analyzed "289 high performance" single nucleotide polymorphisms (SNPs) to test for population admixture among their "European" cohort of participants from St. Louis, Detroit, Minneapolis, and Australia, but found no evidence of population structure. In all these cases, if the investigators found no evidence of population structure using AIMs, they assumed there was none. These results, however, contrast dramatically with the fine-scale mapping of Europeans by Novembre and colleagues (2008) that found identifiable population structure within very narrow geographical areas, emphasizing the high threshold for identifying population structure embedded in the STRUCTURE software program typically used. AIMs are only as robust as the reference population samples used to identify a set of given SNPs as indicative of membership in one ancestral group versus another. Using Yorubas to stand in for all persons of African ancestry (Tishkoff et al., 2009; Bryc et al., 2009) is faulty from the start, as recent research has shown.

These research practices have important ramifications for determining who will benefit from PGx research on addiction. First, the extent to which PGx study results are generalizable to all persons of "European" ancestry is questionable, let alone persons of more distant geographical heritage. What genetic effects might reach the threshold of significance if populations were defined with greater specificity and studies were adequately powered to capture genetic effects among these identifiable subpopulations? An important challenge for PGx research will be to determine which levels of genetic heterogeneity are important to measure for clinical purposes, a calculation that may differ according to phenotype. In the case of PGx research, the importance of identifying individuals at risk of adverse drug events, and the consequences of not identifying such individuals, demands a more fine-grained approach to defining clinically relevant subpopulations than is typically used in current practice.

to discover new ways of framing genetic information about differential risk of illness or response to treatment in ways that transcend the very harmful blunt instrument of traditional racial/ethnic categories. While these categories continue to be a useful bureaucratic tool for tracking health disparities, they are no longer appropriate for use in biomedical research aimed at understanding the etiology of complex diseases such as addiction or factors affecting treatment response.

There is great hope that PGx research will change the landscape of addiction in America by enabling physicians to match individual patients to the substance abuse treatment that will work best for them based on their genetic profile and other information. For this to happen, however, patients must be willing to undergo genetic assessment, physicians must have the capacity and willingness to refer their patients for genetic assessment and execute the tailoring of treatment recommendations, and health insurers must be willing to cover the costs of such services. The more effective PGx treatment strategies are

relative to current strategies, the more important it will be to ensure that minority and underserved populations are able to access them. Otherwise, PGx treatments for addiction will exacerbate already dramatic disparities in the burden of addiction and its impact on individuals' and families' health and horizons of opportunity.

Ensuring that research designs are adequately powered to identify clinically relevant subpopulations in terms of both genetic structure and environmental exposures will be essential to maximizing the benefits and minimizing the harms of PGx research. At the other end of the translational spectrum, once efficacious new treatment strategies for addiction are ready for widespread use, the challenge will be to find creative ways to overcome the disparities in access and quality of care that have forever plagued our health care system. Addiction is a debilitating disease and one that affects not only individuals, but also families and generations to come. Commitment to reaching those communities in greatest need with improved treatments for addiction could go a long way toward addressing these disparities.

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